UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

September 11, 2014

MEMORANDUM

SUBJECT: Petition No. IN-10710: Decision Document for a New Nonfood Use Inert Ingredient, Copper,[29H, 31H-phthalocyaninato(2-)-N29,N30,N31,N32]-, (1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl derivs. (CAS Reg. No. 68411-06-3).

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Executive Summary:

On May 19, 2014 Technology Sciences Group, Inc. on behalf of BASF Corporation, submitted a request to the Environmental Protection Agency, herein referred to as the EPA or the Agency, for the approval of copper,[29H, 31H-phthalocyaninato(2-)-N29,N30,N31,N32]-, (1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl derivs. herein referred to phthalimidomethyl copper phthalocyanine (CAS Reg. No. 68411-06-3) as a nonfood use inert ingredient for use in antimicrobial paint products when applied to surfaces with a limitation of 138 ppm in the end-use product. Phthalimidomethyl copper phthalocyanine's purpose in the formulation is to act as a copper pigment stabilizer in the final antimicrobial paint product. Phthalimidomethyl copper phthalocyanine is currently approved by the United States Food and Drug Administration as a colorant for food contact polymers. The purpose of this document is to assess the risk to human health and the environment from the use of phthalimidomethyl copper phthalocyanine when used as inert ingredient (copper pigment stabilizer) in nonfood use antimicrobial paint products.

Phthalimidomethyl copper phthalocyanine is structurally related to copper phthalocyanine. Phthalimidomethyl copper phthalocyanine consists of the copper phthalocyanine (CAS Reg. No.147-14-8) molecule with a phthalimide (CAS Reg. No. 85-41-6) moiety. Both copper phthalocyanine and phthalimide were previously assessed by the Agency. Copper phthalocyanine is currently approved for food and nonfood use as an inert pesticide ingredient seed treatment under 40 CFR 180.920 and as a colorant in low density plastic films, respectively. Phthalimide is also approved as a nonfood use inert ingredient.

Toxicity data are not available on phthalimidomethyl copper phthalocyanine. It is structurally composed of copper phthalocyanine and phthalimide. Therefore, based on similar structure and physical/chemical properties to copper phthalocyanine and phthalimide, toxicity due to the potential exposure to phthalimidomethyl copper phthalocyanine is expected to resemble that of its individual molecules. Below is a summary of the toxicities of copper phthalocyanine and phthalimide.

Copper phthalocyanine

Copper phthalocyanine exhibits low acute oral toxicity in rabbits and rats with a $LD_{50} \geq 10000$ mg/kg. It is not a skin irritant. Acute oral, dermal and inhalation toxicity studies were not available for review. Dermal sensitization studies were also not available for review.

In a 28-day oral toxicity study in rats, toxicity was manifested as increased organ weights and decreased red blood cell count and tendency to decrease of hemoglobin and packed cell volume in male rats at 1000 mg/kg/day, the limit dose. The No Observed Adverse Effect Level (NOAEL) was 200 mg/kg/day.

In three 13- week feeding studies in rats and mice toxicity was not observed at doses up to 5000 mg per kilogram per day.

A combined reproductive/developmental toxicity study was available for review in rats. Parental, offspring, and developmental toxicity were not observed in the study at doses up to 1000 mg/kg/day.

Tumor formation was not observed in mice following 8 months treatment with copper phthalocyanine. Doses tested were not reported.

The Ames test and some preparation tests available for review. Copper phthalocyanine was not mutagenic in any of the submitted studies.

Neurotoxicity studies were not available for review. However evidence of neurotoxicity was not observed in the submitted studies.

Immunotoxicity studies were not available for review. However evidence of immunotoxicity was not observed in the submitted studies.

Phthalimide

Phthalimide exhibits low acute oral toxicity in rabbits and rats with a $LD_{50} \geq 7940$ mg/kg. It is slightly irritating to the skin and eyes. Acute oral, dermal and inhalation toxicity studies were not available for review. Dermal sensitization studies were also not available for review.

A combined reproductive/developmental toxicity study in rats was available for review as well as several developmental studies in rabbits and hamsters treated with phthalimide. Maternal and reproduction effects were not observed at dose levels up to 1000 mg/kg/day. Developmental effects were observed at dose levels of 500 mg/kg/day in the combined reproductive/developmental toxicity study in rats. Toxicity was manifested as lower body weights or body weight gains in pups during the lactation period at day 4. The NOAEL was 250 mg/kg/day. Maternal and developmental effects were not observed in other studies with rabbits and hamsters.

In a 4 week toxicity study in rats via the inhalation route of exposure, adverse effects were not observed at 0.523 mg/l (~149 mg/kg/day), the highest dose tested.

Phthalimide was negative for mutagenicity in the Ames test, chromosome aberrations test and mouse lymphoma assay.

Neither a dermal toxicity nor a dermal absorption study was available for review for copper phthalocyanine, or phthalimide or phthalimidomethyl copper phthalocyanine, the chemical in question. However, based on the physical characteristics (high molecular weight and high Kow) of phthalimidomethyl copper phthalocyanine significant absorption via the dermal route of exposure is highly unlikely.

Metabolism studies were not available for phthalimidomethyl copper phthalocyanine. However, significant absorption is not expected via the oral, dermal or inhalation routes of exposure due to its large molecular weight, low solubility in water and high kow. Further, if metabolism occurred, the bond most likely broken first would be that between copper phthalocyanine and phthalimide resulting in the release of the individual chemicals.

Dietary exposure is not expected from the use of phthalimidomethyl copper phthalocyanine. Therefore, a dietary risk assessment was not conducted.

For exposure and risk assessment, the oral (200 mg/kg/day) and inhalation 0.523 mg/l (~149 mg/kg/day) endpoints were selected to represent residential and occupational exposures. The oral endpoint was based on increased organ weights and decreased red blood cell count and tendency to decrease of hemoglobin and packed cell volume in male rats observed at 1000 mg/kg/day (limit dose) in a 28-day oral toxicity study in rats treated with copper phthalocyanine. The NOAEL was 200 mg/kg/day. The inhalation endpoint was based on a 4-week toxicity study in rats treated with phthalimide. Adverse effects were not observed at 0.523 mg/l (~149 mg/kg/day), the highest dose tested. Due to the low vapor pressure (9.13×10^{-26} mmHg) and to the very low final use concentration (0.0138%), inhalation exposure and risk are believed to be negligible. In view of the proposed use pattern, dermal exposure is believed to be the significant route of exposure. No

dermal toxicity study is available, therefore, an oral endpoint was used for risk assessment. A dermal absorption rate was assumed to be 100%. Exposure and risk assessments for commercial applicators (painters using airless sprayers) and for "homeowner"/residential applicators resulted in Margins of Exposure greater than 100 which do not exceed the Agency's level of concern.

Phthalimidomethyl copper phthalocyanine is not expected to be toxic to aquatic organisms. It is persistent in the environment. It is not expected to bioaccumulate.

After reviewing the available data, the Agency approves of the non-food use of phthalimidomethyl copper phthalocyanine as an inert ingredient as a copper pigment stabilizer in antimicrobial paint formulations at a final, end-use product concentration not to exceed 138 ppm (0.0138%).

Background

On May 19, 2014 Technology Sciences Group, Inc. on behalf of BASF Corporation, submitted a request to the Environmental Protection Agency, herein referred to as the EPA or the Agency, for the approval of copper,[29H, 31H-phthalocyaninato(2-)-N29,N30,N31,N32]-,(1,3-dihydro-1,3-dioxo-2Hisoindol-2-yl)methyl derivatives herein referred to phthalimidomethyl copper phthalocyanine (CAS Reg. No.68411-06-3) as a nonfood use inert ingredient for use in antimicrobial paint products when applied to surfaces with a limitation of 138 ppm in the end-use product. Phthalimidomethyl copper phthalocyanine's purpose in the formulation is to act as a copper pigment stabilizer in the final antimicrobial paint product. Phthalimidomethyl copper phthalocyanine is currently approved by the United States Food and Drug Administration as a colorant for food contact polymers.

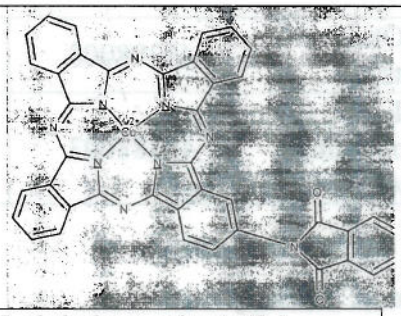
Phthalimidomethyl copper phthalocyanine is structurally related to copper phthalocyanine. Phthalimidomethyl copper phthalocyanine consists of the copper phthalocyanine (CAS Reg. No.147-14-8) molecule with a phthalimide (CAS Reg. No.85-41-6) moiety. Its toxicity is expected to resemble that of these individual molecules. Both copper phthalocyanine and phthalimide were previously assessed by the Agency. Copper phthalocyanine is currently approved for food and nonfood use as an inert pesticide ingredient seed treatment under 40 CFR 180.920 and as a colorant in low density plastic films, respectively. Phthalimide is also approved for nonfood use.

Physical Chemical Properties

Some of the physical and chemical characteristics of phthalimidomethyl copper phthalocyanine (CAS Reg. No. 68411-06-3) are found in Table 2. Data were reproduced from the applicant's submission (MRID 4938801).

Table 1: Physical/Chemical Properties of Phthalimidomethyl Copper Phthalocyanine

Parameter	Value	Source

Structure		
Chemical Name	Copper,[29H, 31H-phthalocyaninato(2-)-N29,N30,N31,N32]-,(1,3-dihydro-1,3-dioxo-2Hisoindol-2-yl)methyl derivatives	MRID 49388001
CAS #	68411-06-3	
Common names	phthalimidomethyl copper phthalocyanine	
Molecular Weight (Daltons)done	735	
Physical State	solid	
Melting Point (C°)	394.84	
Boiling Point (C°)	1009.53	
Log Kow	9.93	
Water Solubility (mg/L @ 25C°)	5.2E-9	
Henry's Law Constant (atm-m^3/mole)	1.698E-17	
Vapor Pressure (mm Hg @25C°)	9.13E-26 mmHg	

HAZARD CHARACTERIZATION

Toxicity data is not available on phthalimidomethyl copper phthalocyanine. However, toxicity due to potential exposure is expected to resemble that of its individual molecules, copper phthalocyanine and phthalimide. Below is a summary of the toxicities of copper phthalocyanine and phthalimide. Data were reproduced from the applicant's submission (MRIDs 49388001, 49388002 and 49388003).

Copper Phthalocyanine

Acute Toxicity

Table 2: Acute Toxicity Data Copper Phthalocyanine

Study Type	MRID #	Results	Toxicity Category
Acute Oral (Rats)	49388003	LD_{50}= 10000 mg/kg	IV

Acute Oral (Rabbits)	49388003	LD_{50} (male)= 16000 mg/kg	IV
Dermal Irritation(animal unknown)	49388003	Not an irritant	Unknown

Subchronic Toxicity

In a thirteen week feeding study, mice were treated with a dosage of 5000 mg/kg/day of copper phthalocyanine. No toxic signs or pathological changes were found after 13 weeks of testing. No other data were provided (MRID 49388003).

In another 13 week feeding study, rats and mice (strains not recorded) were administered 0.3-5.0% (~ 30-5,000 mg/kg/day) of copper phthalocyanine. No toxic signs or pathological changes were found after 13 weeks of testing. No other data were provided (MRID 49388003).

In a 28 day repeated dose toxicity study Wistar rats (10/sex/dose) were treated via gavage with 0, 40, 200 and 1,000 mg/kg/day of copper phthalocyanine. A significant decrease of red blood cell count and tendency to decrease of hemoglobin and packed cell volume were detected in male rats at 200 and 1,000 mg/ kg. There was an increase in organ weight in lungs, spleen, adrenal and salivary glands at 1,000 mg/kg/day in male rats. In female rats, there was slight increase in erythroblasts at 1000 mg/kg/day. The NOAEL was 200 mg/kg/day. The LOAEL was 1000 mg/kg/day based on increased organ weights and decreased red blood cell count and tendency to decreased hemoglobin and packed cell volume in male rats (MRID 49388003).

Developmental/Reproduction Toxicity

In the combined reproductive/developmental toxicity study, crj, CD(SD) rats (12/sex/dose) were treated with 0, 40, 200 and 1,000 mg/kg/day of copper phthalocyanine through day 3 of lactation. There were no teratogenic effects observed under the test conditions used. Parental, offspring and reproduction toxicity were not observed at 1000 mg/kg/day, the highest dose tested (MRID 49388003).

Carcinogenicity Toxicity

In an 8 month oral toxicity study in mice, copper phthalocyanine did not cause tumor formation. No other data were provided (MRID 49388003).

In another 8-month study in mice, copper phthalocyanine was administered to mice 34 times/week at 0.5mg/animal. Tumors were not observed. No other data were provided (MRID 49388003).

Mutagenicity

In an Ames test, *Salmonella typhimurium* strains TA98, TA100, TA102 and TA97 were treated with copper phthalocyanine with and without metabolic activation. The assay was negative for mutagenicity. No other data were provided (MRID 49388003).

In a second Ames test, *Salmonella typhimurium* strainsTA1538 and TA1535 were treated with copper phthalocyanine with and without metabolic activation. The assay was negative for mutagenicity. No other data were provided (MRID 49388003).

In a third Ames test, *Salmonella typhimurium* strains TA98 and TA100 were treated with copper phthalocyanine with and without metabolic activation. The assay was negative for mutagenicity. No other data were provided (MRID 49388003).

In an *in vitro* chromosome aberration test, Chinese hamster ovary (CHO) cells were incubated with 0, 0.75, 1.50, and 3.0 mg/mL of copper phthalocyanine with and without metabolic activation. The test substance was negative for mutagenic effect under the test conditions used (MRID 49388003).

Neurotoxicity

There are no neurotoxicity studies available in the database; however, the available toxicity data for copper phthalocyanine shows no evidence for neurotoxic effects and therefore, the Agency does not believe that copper phthalocyanine would be neurotoxic.

Table 3. Toxicology Profile for Copper Phthalocyanine

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
28-Day Oral Toxicity-rats	0, 40, 200 and 1,000 mg/kg/day	NOAEL = 200 mg/kg/day. LOAEL = 1000 mg/kg/day based on increased organ weights and decreased red blood cell count and tendency to decreased hemoglobin and packed cell volume in male rats.
13-Week Oral Toxicity Study-mice	5000 mg/kg/day	NOAEL = 5000 mg/kg/day.
13-Week Oral Toxicity Study-rats and mice	30-5000 mg/kg/day	NOAEL = 5000 mg/kg/day.
Combined Reproductive/Developmental Toxicity Study-rats	0, 40, 200 and 1,000 mg/kg/day	Parental NOAEL = 1000 mg/kg/day. Parental LOAEL was not established. Reproduction NOAEL = 1000 mg/kg/day Reproduction LOAEL was not established. Developmental NOAEL = 1000 mg/kg/day. Developmental LOAEL was not established.

Table 3. Toxicology Profile for Copper Phthalocyanine		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
8 Month Oral Toxicity Study-mice	Unknown	Tumor formation not observed.
8 Month Toxicity Study-Subcutaneous-mice	0.5 mg/animal	Tumor formation not observed.
Ames Test	Unknown	Negative
Ames Test	Unknown	Negative
Ames Test	Unknown	Negative
Chromosome Aberration Test- Chinese hamster ovary cells	0, 0.75, 1.50, and 3.0 mg/mL	Negative

Phthalimide

Combined Repeated Dose/Reproduction-rat

In a OECD combined repeated dose/reproduction toxicity study, Crj: CD(SD) rats (12/sex/dose) were administered phthalimide (0, 250, 500, 1000 mg/kg bw/day) via gavage for 46 days (male rats), from 14 days before mating to day 3 of lactation (female rats).

No effects of phthalimide were detected on general appearance, body weight, food consumption, organ weights, autopsy, gross pathology, urinalysis, hematology or biochemical parameters, or histopathological findings in males. One female at 1000 mg/kg bw/day exhibited decreased body weight and food consumption, periportal fatty change in the liver, renal epithelial fatty change, and atrophy in the thymus. The incidences of periportal fatty change in the liver and atrophy in the thymus were within the historical control ranges for these effects (0.4 and 4.3%,

respectively). The historical control range for the incidence of renal epithelial fatty change was 0%. Treatment related effects were not observed in the other female rats.

The parental NOAEL for repeat dose toxicity in rats was considered to be ≥1000 mg/kg bw/day, the highest dose tested (MRID 49388002).

Reproduction Toxicity

In a OECD combined repeated dose and reproduction /reproduction toxicity study, Crj: CD(SD) rats (12/sex/dose) were administered phthalimide (0, 250, 500, 1000 mg/kg bw/day) via gavage for 46 days (male rats), from 14 days before mating to day 3 of lactation (female rats).

No effects were observed in any dose levels in males. One female in the 500 mg/kg bw/day dose group did not deliver until day 26 of gestation. Autopsy of the female revealed dilatation of the uterus and vagina, and five implantation sites.

Body weights and food consumption were decreased in one female dosed with 1000 mg/kg bw/day which demonstrated abnormal findings on histopathological examination. Eight of its pups were dead or cannibalized, and the surviving nine pups showed body weight loss.

Historical control data on reproductive outcome in this strain of rats in the laboratory that performed this screening reproductive toxicity study are as follows: dilatation of the uterine horn: 0-4.2% (average=0.6%); dilatation of the uterine cervix: 0-4.0% (average= 0.3%); dilatation of the vagina: 0%.

One female did not deliver at 500 mg/kg. No offspring were found in this female on gestation day 2. Only 5 implantation sites were found in this female. Historical control data on reproductive outcome in this strain of rats in the laboratory performed this screening reproductive toxicity study are follows: fertility index (No. of pregnant animals/No. of pairs with successful copulation) x 100: 91.7-100% (average=96.5%); gestation index (No. of females with live pups delivered/No. of pregnant females) x 100: 95.5-100% (average=99.0%); fertility index at 1000 mg/kg was 83.3% in this study. This value was not within the range of the historical control data; however, it is not significantly different from the control value of this study.

The reproduction NOAEL for reproductive toxicity in rats was considered to be 1000 mg/kg/day (MRID 49388002).

Developmental Toxicity

Male and female pups of the 500 and 1000 mg/kg bw/day groups showed lower body weights or body weight gains in the lactation period at day 4 (not at day 0, and 1). No pups with malformation were found in any group. No changes in pathological findings were observed in offspring.

The influence of phthalimide on developmental performance was as follows: no influence on number of dead pups, number of pups born, sex ratio, gestation length, gestation index, nursing

index, live pups on day 4. Male and female pups of the 500 and 1000 mg/kg bw/day treatment groups showed lower body weights or body weight gains in the lactation period. On the basis of these findings, the NOAEL of phthalimide for developmental toxicity of male and female pups was 250 mg/kg bw/day.

The NOAEL for developmental toxicity was considered to be 250 mg/kg/day. The developmental LOAEL was 500 mg/kg bw/day based on slightly lower body weights or body weight gains in pups during the lactation period at day 4 (not at day 0, and 1) (MRID 49388002).

Rabbit:

In a developmental toxicity study, New Zealand white and Chinchilla rabbits (3/sex/dose) were treated via gavage with 150 mg/kg/day of phthalimide on gestation days 7-12. On the 28th day rabbits were killed and the fetuses removed. Fetuses were examined for gross external malformations, particularly those involving the head and limbs, number of animals, implantations, resorptions. No evidence for embryotoxic or teratogenic activity was found. The NOAEL was 150 mg/kg/day, the only dose tested.

In another developmental toxicity study, Dutch Belted rabbits were treated via gelatin capsules with 75 mg/kg/d of phthalimide on gestation days 6-16. Animal body weight was measured every third day and provided a basis for changing dosages (75 mg/kg bw/day throughout the experiment). On day 29 animals were killed, the uterus was examined and opened, and fetuses were excised and examined for the presence of resorption sites. Pups were weighed, crown-to-rump length was measured and each fetus was carefully examined for gross structural malformations. Internal structures were examined by dissection. There was no difference in the gestational weight gain and no maternal fatality of the dams dosed with phthalimide (n = 10) compared to the control group (n = 7). No significant difference was seen for the total number of implantations (66 and 52 for phthalimide group and control, respectively), average no. of implantations (6.6 and 7.4), number of resorptions (3 and 0), average litter size (6.3 and 7.4), and number of malformed fetuses 0 and 1). The maternal and developmental NOAELs were 150 mg/kg/day, the only dose tested (MRID 49388002).

Hamster:

In another developmental toxicity study, Golden Syrian hamsters were administered a single oral (unspecified) dose of phthalimide (0, 250, 500 or 1000 mg/kg) in (carboxymethylcellulose) on gestation day 7 or 8. On day 15 the animals were killed, the uteri were opened and examined for the presence of resorption sites. The fetuses were removed, weighed, examined for external malformation, and checked for viability. Fetuses showing gross abnormalities were further examined. Neither maternal toxicity nor teratogenic effects were observed in all dose groups. The maternal and developmental NOAELs were 1000 mg/kg, the highest dose tested (MRID 49388002).

Chicken:

In another developmental toxicity study, chicken embryos were injected with a single dose of phthalimide (3, 6, 10-12, and 18-20 mg/kg) into either the yolk or air cell of fresh fertile White

Leghorn eggs before incubation. The compound was injected in a total volume of 0.05 ml per egg or less into groups of 20 to 50 eggs per dose level (dose levels: 3, 6, 10-12 or 18-20 ppm (mg/kg) in the egg). Eggs were incubated at 38 °C and 60% relative humidity for 21 days until hatch. Nonviable embryos and the hatched chicks were examined for gross skeletal abnormalities. The mortality in chicken embryos was 0, 0, 5, and 24% in the presence of 3, 6, 10-12, and 18-20 mg/kg of phthalimide, respectively. For the volumes of solvent (DMSO) used in these experiments, the background mortality averaged 15 per cent, with a range of 0 to 25%. Hence, mortality values of less than 25% indicate little or no toxic effects attributed to phthalimide. In the chicken embryos phthalimide produced a low incidence of specific malformations. The percentage of incidence of malformations found for the total number of eggs (305) injected with phthalimide was 3.93 %, the percentage of incidence in the control groups was < 2%. In the case of phthalimide, the malformations occurred in head, legs and lower body (the data include both yolk- and air cell-injected eggs, since the occurrence of malformed embryos was independent of the injection route used). There was no correlation between teratogenic effects and dose level (MRID 49388002).

4 Week Toxicity Study-Inhalation, Rat

In a 4 -week, Sprague-Dawley rats (20/sex/dose) were treated via the inhalation route of exposure with 0.051, 0.154 or 0.523 mg/l (~15, 44 or 149 mg/kg/day) of phthalimide. Animals were exposed for six hours per day, five days per week, four weeks; a total of 20 exposures. Animals were exposed in specially constructed stainless steel and glass whole-body inhalation chambers. Nitrogen gas and additional airflow rates were maintained at 7 and 40 liters per minute, respectively. The concentration of the test material fumes present in the exposure chambers were measured by sampling the test atmosphere in the breathing zones of the animals being exposed by gas chromatography. The following parameters were evaluated: mortality, behavioral reactions, body weight, hematology, clinical chemistry, urinalyses and pathology.

Treatment related effects were not observed in male rats with regard to mortality, behavioral reactions, body weight, body weight gain, hematology, clinical chemistry, urinalyses or pathology. The same is true for female rats except a significant dose dependent decrease in absolute (2.200 (control), 1.728 (21%), 1.640 (25%), and 1.576 g (28%) and relative (1.093 (control), 0.8703 (20%), 0.8069 (26%), 0.7276 (33%) lung weights was observed in all treatment groups. Histopatholgic examination of the rats in the control and high dose groups did not reveal treatment related effects. The NOAEL was 0.523 mg/l (~149 mg/kg/day), the highest dose tested (MRID 49388002).

Mutagenicity

In an Ames test, *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 were treated with 8, 40, 200, 1000 or 5000 ug/plate (plate incorporation method); 8, 40, 200, 1000 or 5000 ug/tube (preincubation method) of phthalimide with and without metabolic activation. The positive controls used in these experiments were sodium azide, nitrofurantoin, 4-nitro-1,2-phenylene diamine and 2-aminoanthracene. Neither the *Salmonella*/microsome plate incorporation test nor the *Salmonella*/microsome preincubation test, employing doses of up to 5000 ug per plate or incubation of phthalimide, respectively, showed any evidence of mutagenic activity in the

absence and presence of metabolic activator, respectively. Doses of up to 5000 ug per plate or per incubation did not cause any bacteriotoxic effects. The positive controls had a marked mutagenic effect, as was seen by a significant increase in mutant colonies compared to the corresponding negative controls (MRID 49388002).

In another Ames test, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 *E. coli* WP2 uvrA were treated with 313, 625, 1250, 2500, 5000 ug/plate phthalimide in dimethyl sulfoxide. No cytotoxicity was observed up to 5000 ug/plate, the highest concentration tested. Mutagenicity was not observed (MRID 49388002).

In a chromosomal aberration test, Chinese hamster CHL/IU cells were treated with 0, (313), 625, 1250, 2500, 5000 ug/ml of phthalimide with and without metabolic activation. The solvent was 1% Carboxymethylcellulose-sodium. Treatments were conducted as follows: -S9-mix 24hr continuous: 2356 ug/mL; -S9-mix 48hr continuous: 2540 ug/mL, -S9-mix 6hr short term : 991 ug/mL, +S9-mix 6hr short term : 4524 ug/mL. At short term treatment with S9-mix, slight structural aberration was observed at 2500 ug/ml (6%) and 5000 ug/ml (10%). Structural aberrations at any other concentration were within 5% (negative). Polyploidy was not dose dependently induced in any treatment group. Except for short term treatment without S9 mix, remarkable aberration was observed in positive controls. Cytotoxicity evident by growth inhibition (10% of control) was observed at the 6 hour treatment period without S9 mix. Phthalimide did not induce polyploidy at any concentration. Weak induction of structural chromosomal aberration were observed only at high concentrations where cytotoxicity was seen in parallel. Therefore, this substance is considered to be not clastogenic (MRID 49388002).

In a mouse lymphoma assay, L5178Y mouse lymphoma cells were treated with 65, 130, 260, 520 or 1040 ug/ml of phthalimide with and without metabolic activation. Positive controls were ethylmethansulfonate and dimethylnitrosamine, which requires metabolic activation. No dose related toxicity was observed although the viable counts were lower at the high level phthalimide concentration (viable counts at 1040 ug/ml: 90%). The compound did not induce significant increase in mutant frequencies at any concentration tested (65-1040 ug/ml) in the absence or presence of S9-mix. Negative and positive controls gave the expected results (MRID 49388002).

Dermal Toxicity and Dermal Absorption

Neither a dermal toxicity nor a dermal absorption study was available for review for copper phthalocyanine, phthalimide or phthalimidomethyl copper phthalocyanine, the chemical in question. However, based on the physical characteristics (high molecular weight and high Kow) of phthalimidomethyl copper phthalocyanine significant absorption via the dermal route of exposure is highly unlikely.

Metabolism

Metabolism studies were not available for phthalimidomethyl copper phthalocyanine. However, significant absorption is not expected via the oral, dermal or inhalation routes of exposure due to its high molecular weight, low solubility in water and high Kow. Further, if

metabolism occurred, the bond most likely broken first would be that between copper phthalocyanine and phthalimide resulting in the release of the individual chemicals.

Table 4. Toxicology Profile for Phthalimide

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
4 Week Inhalation Toxicity Study-rat	0.051, 0.154 or 0.523 mg/l (~15, 44 or 149 mg/kg/day)	NOAEL = 0.523 mg/l (~149 mg/kg/day). LOAEL was not established.
Combined Reproductive/Developmental Toxicity Study-rats	0, 250, 500, 1000 mg/kg/day	Parental NOAEL = 1000 mg/kg/day. Parental LOAEL was not established. Reproduction NOAEL = 1000 mg/kg/day Reproduction LOAEL was not established. Developmental NOAEL = 250 mg/kg/day. Developmental LOAEL = 500 mg/kg/day based on slightly lower body weights or body weight gains in pups during the lactation period at day 4.
Developmental Toxicity - New Zealand white and Chinchilla rabbits -gavage	150 mg/kg/day	Maternal NOAEL = 150mg/kg/day. Maternal LOAEL was not established. Developmental NOAEL = 150 mg/kg/day. Developmental LOAEL was not established.
Developmental Toxicity - Dutch Belted-rabbits - gavage	75 mg/kg	NOAEL = 75 mg/kg/day. LOAEL was not established.
Developmental Toxicity – Golden Syrian-Hamsters – Acute oral	0, 250, 500 or 1000 mg/kg	NOAEL = 1000 mg/kg. LOAEL was not established.
Developmental Toxicity – Chicken Embryo- Acute oral	3, 6, 10-12, and 18-20 mg/kg	NOAEL = 20 mg/kg. LOAEL was not established.
Ames Test	8, 40, 200, 1000 or 5000 ug/plate (plate incorporation method) 8, 40, 200, 1000 or 5000 ug/tube (preincubation method)	Negative

Table 4. Toxicology Profile for Phthalimide		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Ames Test	313, 625, 1250, 2500, 5000 ug/plate	Negative.
Chromosomal Aberration Test	0, (313), 625, 1250, 2500, 5000 ug/ml	Not Clastogenic.
Mouse Lymphoma Assay	65, 130, 260, 520 or 1040 ug/ml	Negative.

Toxicity Endpoint Selection

Table 5. Summary of Toxicological Doses and Endpoints for Phthalimidomethyl Copper Phthalocyanine for Use in Human Health Risk Assessment			
Exposure/Scenario	Point of Departure and Uncertainty/Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Dermal short-, intermediate- and long-term (1 to 30 days, 1 to 6 months and >6 months)	NOAEL = 200 mg/kg/day UF_A = 10x UF_H = 10x FQPA SF = 1x	LOC for MOE = 100	28-Day Oral Toxicity Study-rat LOAEL = 1000 mg/kg/day based increased organ weights and decreased red blood cell count and tendency to decrease of hemoglobin and packed cell volume in male rats.
Inhalation short-, intermediate- and long-term (1 to 30 days, 1 to 6 months and >6 months)	NOAEL = 149 mg/kg/day (Inhalation absorption rate = 100%) UF_A = 10x UF_H = 10x FQPA SF = 1x	LOC for MOE = 100	4-Week Inhalation Toxicity Study-rat LOAEL was not established.
Cancer (Oral, dermal, inhalation)	Based on the lack of tumor formation in a chronic/carcinogenicity study and the lack of mutagenicity, phthalimidomethyl copper phthalocyanine is considered not likely to be carcinogenic.		

Since dietary exposure is not expected endpoints were not selected for the acute and chronic dietary exposure scenarios. Also, an endpoint was not selected for non-dietary oral exposure since hand to mouth scenarios are not anticipated based on the proposed use pattern. In addition, the physical/chemical properties (high molecular weight and high lipophilicity) of phthalimidomethyl copper phthalocyanine indicate that significant absorption via the oral route of exposure is not

likely to occur. Thus, in the absence of dermal toxicity data, the 28-day oral toxicity study in rats was selected for the dermal exposure scenario. Toxicity was manifested as increased organ weights and decreased red blood cell count and tendency to decrease of hemoglobin and packed cell volume in male rats at 1000 mg/kg/day (limit dose). The NOAEL was 200 mg/kg/day. The dermal absorption rate was assumed to be 100%. There were several studies with lower NOAELs; however, these NOAELs were not selected because they were considered an artifact of the dose spread.

The 4-week toxicity study in rats via the inhalation route of exposure was selected to assess inhalation exposure. Toxicity was not observed at concentrations up to 0.523 mg/l (~149 mg/kg/day), the highest dose tested. This study represents the lowest NOAEL in the database in the most sensitive species.

Exposure Assessment

Exposure to phthalimidomethyl copper phthalocyanine is expected during the paint formulation process or during application of the final end-use paint formulation either on a commercial/occupational basis or on a non-commercial (residential) basis. Exposures during the formulation process are under the aegis of the Occupational Safety and Health Administration (OSHA) thus are not further considered herein. Individuals applying the final end-use paint formulation may be exposed during the application process whether by brush application, "roll-on" application, or spray application.

Individuals involved in commercial/occupational exposures are typically protected by engineering controls (i.e., coveralls, dust masks) as a result of commercial paint application regulations for protection from solvents and other volatile materials. Although the Agency believes the potential is low for biologically significant exposure to phthalimidomethyl copper phthalocyanine, the Agency has conducted an exposure and risk assessment for commercial applicators (i.e. painters) and for homeowner/residential applicators. The assessment methodologies are standard risk assessment techniques developed by the Science Advisory Committee for Exposure (EXPOSAC) Health Effects Division, Office of Pesticide Programs/EPA.

For this assessment it is assumed that the density of a typical paint product containing phthalimidomethyl copper phthalocyanine is 10.0 lb/gallon;
Amount phthalimidomethyl copper phthalocyanine in the formulated product = 138 ppm (0.0138%)
10.0 lb of formulation/gal * 0.0138 (%) material = 0.138 lb/gal material (inert)
Toxicological endpoint is 200 mg/kg/day for dermal exposure and 149 mg/kg/day for inhalation exposure;
Dermal and inhalation absorption are 100 %;
2.94 gallons of paint are applied/day;
Body weight is 80 kg;
Personal Protective Equipment (PPE) = double layer work clothing (coveralls over work clothes), protective gloves NO respiratory protection
Method of application = Airless spray gun.
Unit exposures are taken from the Pesticide Handlers Exposure Database (PHED) Occupational

Pesticide Handler Unit Exposure Surrogate Reference Table, March 2012
Dermal Unit Exposure (U.E.) = 10.6 mg/lb handled
Inhalation U.E. = 0.56 mg/lb handled

Table 6 Estimated Exposure and Risk to Commercial Applicators Exposed to Phthalimidomethyl Copper Phthalocyanine In Antimicrobial Paint Formulations

Unit Exposure[1] Mg inert/lb handled	Applic. Rate[2] lb ai/gal	Units Treated[3]	Avg. Daily Exposure[4] mg/kg bw/day	MOE[5]
Dermal: Dbl Layer with gloves 10.6 Inhal. 0.056	0.138 lb/gal	2.94gal/day	Dermal: 0.054 Dbl Layer with gloves Inhalation: 0.00028	Dermal 3,703 Inhalation 532,143

1. Unit Exposures are taken from (Occupational Pesticide Handler Unit Exposure Surrogate Reference Table, March 2012).

Dermal = Double Layer Work Clothing with use of protective gloves; Inhal. = Inhalation. Units = mg inert/pound of inert ingredient handled.

2. Applic. Rate. = Density of the paint product x amount of the inert ingredient in the paint product.
3. Units Treated is assumed value.
4. Average Daily Exposure = Unit Exposure * Applic. Rate * Units Treated * 100 % dermal absorption (100% inhalation absorption) ÷ **80** kg Body Weight
5. MOE = Margin of Exposure = NOAEL ÷ ADE.

Dermal MOE = 200 mg/kg/day ÷ 0.054 mg/kg/day = 3,703
Inhalation MOE = 149mg/kg/day ÷ 0.00028mg/kg/day = 532,143

Typically, Margins of Exposure (MOE) ≥ 100 do not exceed the Agency's level of concern. In this case MOEs are greater than 100 using conservative assumptions (100% dermal and inhalation absorption and assuming NO respiratory protection).

An estimate of "homeowner"/residential exposure and risk is presented below. The assessment methodology is the same except the Unit Exposures are for persons wearing a single layer of work clothing, NO protective gloves and NO respiratory protection. It is further assumed that the residential applicator applies the same amount of paint per day as reported for commercial applicators. It is assumed that a residential applicator uses a brush or roller as the method of application.

Table 7 Estimated Exposure and Risk to "Residential" Applicators Exposed to Phthalimidomethyl Copper Phthalocyanine In Antimicrobial Paint Formulations

Unit Exposure[1] mg inert/lb handled	Applic. Rate[2] lb ai/gal	Units Treated[3]	Avg. Daily Exposure[4] mg/kg bw/day	MOE[5]
Dermal: Dbl Layer with gloves 180.0	0.138 lb/gal	2.94gal/day	Dermal: 0.913 Dbl Layer with gloves	Dermal 219 Inhalation

Inhal.	0.28			Inhalation: 0.0014	106,429

1. Unit Exposures are taken from (Occupational Pesticide Handler Unit Exposure Surrogate Reference Table, March 2012).

Dermal = Single Layer Work Clothing NO protective gloves; Inhal. = Inhalation. Units = mg inert/pound of inert ingredient handled.

2. Applic. Rate. = Density of the paint product x amount of the inert ingredient in the paint product.
3. Units Treated is assumed value.
4. Average Daily Exposure = Unit Exposure * Applic. Rate * Units Treated * 100 % dermal absorption (100% inhalation absorption) ÷ 80 kg Body Weight
5. MOE = Margin of Exposure = NOAEL ÷ ADE.

Dermal MOE = 200 mg/kg/day ÷ 0.913 mg/kg/day = 219
Inhalation MOE = 149 mg/kg/day ÷ 0.0014 mg/kg/day = 106,429

The estimated MOEs for residential handlers are greater than 100 which do not exceed the Agency's level of concern. The estimated exposures and risks were based on highly conservative assumptions: 100 % absorption via the dermal and inhalation routes of exposure; one layer of work clothing; NO protective gloves; NO respiratory protection; a commercial daily rate of application (2.94 gal/day).

Ecotoxicity

Ecotoxicity data were not available on phthalimidomethyl copper phthalocyanine. However, data on copper phthalocyanine, was used to describe ecotoxicity.

Phthalimidomethyl copper phthalocyanine has low water solubility and a high Koc; in water. It is expected to be adsorbed to sediment and other available surfaces suggesting low bioavailability to aquatic organisms. OECD (1993) reported on an acute aquatic toxicity test for copper phthalocyanine, a close structural surrogate of phthalimidomethyl copper phthalocyanine. The 48-hour LC_{50} of copper phthalocyanine in orange-red killifish (Oryzias latipes) was greater than 100 mg/l, indicating negligible aquatic toxicity. A similar aquatic toxicity scenario is likely for phthalimidomethyl copper phthalocyanine (MRID .49388001).

Environmental Fate and Effects

The applicant submitted environmental fate and effects data modeled with the US EPA's EPI Suite EPIWIN program. The results were summarized as follows. Phthalimidomethyl copper phthalocyanine is persistent in the environment, except for the atmosphere. The environmental fate is primarily controlled by its large molecular size, high Kow (Kow = 9.93), and ionic nature. If released to soil, phthalimidomethyl copper phthalocyanine will tend to adsorb strongly to soil particles as indicated by its high Koc = 7.85×10^5 L/kg (soil adsorption coefficient), with negligible mobility through soil to ground water. Almost no volatilization is expected from water; rather phthalimidomethyl copper phthalocyanine will adsorb strongly to sediment and other

available surfaces in the water, with limited biodegradation taking place very slowly. Hydrolysis is not expected to be an important environmental fate process. The bioconcentration potential is considered low when the bioconcentration factor (BCF) is less than 1000, suggesting that this compound will not bioconcentrate in aquatic organisms. Theoretically, aquatic organisms may still be exposed to phthalimidomethyl copper phthalocyanine through the diet, i.e. via ingesting particles onto which the compound is bound, a scenario not accounted for in the BCF. However, because the concentration of phthalimidomethyl copper phthalocyanine is so low in the final product formulation (138 ppm maximum), uptake by aquatic organisms is not expected to be significant via particle ingestion or any other route. Furthermore, the BCF of copper phthalocyanine, a structurally related chemical, is 0.33-11 (EPA 2009) in fish suggesting very low bioconcentration potential (MRID .49388001).

Risk Characterization

On May 19, 2014 Technology Sciences Group, Inc. on behalf of BASF Corporation, submitted a request to the Environmental Protection Agency, herein referred to as the EPA or the Agency, for the approval of copper,[29H, 31H-phthalocyaninato(2-)-N29,N30,N31,N32]-, (1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl derivs. herein referred to phthalimidomethyl copper phthalocyanine (CAS Reg. No. 68411-06-3) as a nonfood use inert ingredient for use in antimicrobial paint products when applied to surfaces with a limitation of 138 ppm in the end-use product. Phthalimidomethyl copper phthalocyanine's purpose in the formulation is to act as a copper pigment stabilizer in the final antimicrobial paint product. Phthalimidomethyl copper phthalocyanine is currently approved by the United States Food and Drug Administration as a colorant for food contact polymers. The purpose of this document is to assess the risk to human health and the environment from the use of phthalimidomethyl copper phthalocyanine when used as inert ingredient (copper pigment stabilizer) in nonfood use antimicrobial paint products.

Phthalimidomethyl copper phthalocyanine is structurally related to copper phthalocyanine. Phthalimidomethyl copper phthalocyanine consists of the copper phthalocyanine (CAS Reg. No.147-14-8) molecule with a phthalimide (CAS Reg. No. 85-41-6) moiety. Both copper phthalocyanine and phthalimide were previously assessed by the Agency. Copper phthalocyanine is currently approved for food and nonfood use as an inert pesticide ingredient seed treatment under 40 CFR 180.920 and as a colorant in low density plastic films, respectively. Phthalimide is also approved as a nonfood use inert ingredient.

Toxicity data are not available on phthalimidomethyl copper phthalocyanine. It is structurally composed of copper phthalocyanine and phthalimide. Therefore, based on similar structure and physical/chemical properties to copper phthalocyanine and phthalimide, toxicity due to the potential exposure to phthalimidomethyl copper phthalocyanine is expected to resemble that of its individual molecules. Below is a summary of the toxicities of copper phthalocyanine and phthalimide.

Copper phthalocyanine

Copper phthalocyanine exhibits low acute oral toxicity in rabbits and rats with a $LD_{50} \geq 10000$ mg/kg. It is not a skin irritant. Acute oral, dermal and inhalation toxicity studies were not available for review. Dermal sensitization studies were also not available for review.

In a 28-day oral toxicity study in rats, toxicity was manifested as increased organ weights and decreased red blood cell count and tendency to decrease of hemoglobin and packed cell volume in male rats at 1000 mg/kg/day, the limit dose. The No Observed Adverse Effect Level (NOAEL) was 200 mg/kg/day.

In three 13- week feeding studies in rats and mice toxicity was not observed at doses up to 5000 mg per kilogram per day.

A combined reproductive/developmental toxicity study was available for review in rats. Parental, offspring, and developmental toxicity were not observed in the study at doses up to 1000 mg/kg/day.

Tumor formation was not observed in mice following 8 months treatment with copper phthalocyanine. Doses tested were not reported.

The Ames test and some preparation tests available for review. Copper phthalocyanine was not mutagenic in any of the submitted studies.

Neurotoxicity studies were not available for review. However evidence of neurotoxicity was not observed in the submitted studies.

Immunotoxicity studies were not available for review. However evidence of immunotoxicity was not observed in the submitted studies.

Phthalimide

Phthalimide exhibits low acute oral toxicity in rabbits and rats with a $LD_{50} \geq 7940$ mg/kg. It is slightly irritating to the skin and eyes. Acute oral, dermal and inhalation toxicity studies were not available for review. Dermal sensitization studies were also not available for review.

A combined reproductive/developmental toxicity study in rats was available for review as well as several developmental studies in rabbits and hamsters treated with phthalimide. Maternal and reproduction effects were not observed at dose levels up to 1000 mg/kg/day. Developmental effects were observed at dose levels of 500 mg/kg/day in the combined reproductive/developmental toxicity study in rats. Toxicity was manifested as lower body weights or body weight gains in pups during the lactation period at day 4. The NOAEL was 250 mg/kg/day. Maternal and developmental effects were not observed in other studies with rabbits and hamsters.

In a 4 week toxicity study in rats via the inhalation route of exposure, adverse effects were not observed at 0.523 mg/l (~149 mg/kg/day), the highest dose tested.

Phthalimide was negative for mutagenicity in the Ames test, chromosome aberrations test and mouse lymphoma assay.

Neither a dermal toxicity nor a dermal absorption study was available for review for copper phthalocyanine, or phthalimide or phthalimidomethyl copper phthalocyanine, the chemical in question. However, based on the physical characteristics (high molecular weight and high Kow) of phthalimidomethyl copper phthalocyanine significant absorption via the dermal route of exposure is highly unlikely.

Metabolism studies were not available for phthalimidomethyl copper phthalocyanine. However, significant absorption is not expected via the oral, dermal or inhalation routes of exposure due to its large molecular weight, low solubility in water and high kow. Further, if metabolism occurred, the bond most likely broken first would be that between copper phthalocyanine and phthalimide resulting in the release of the individual chemicals.

Dietary exposure is not expected from the use of phthalimidomethyl copper phthalocyanine. Therefore, a dietary risk assessment was not conducted.

For exposure and risk assessment, the oral (200 mg/kg/day) and inhalation 0.523 mg/l (~149 mg/kg/day) endpoints were selected to represent residential and occupational exposures. The oral endpoint was based on increased organ weights and decreased red blood cell count and tendency to decrease of hemoglobin and packed cell volume in male rats observed at 1000 mg/kg/day (limit dose) in a 28-day oral toxicity study in rats treated with copper phthalocyanine. The NOAEL was 200 mg/kg/day. The inhalation endpoint was based on a 4-week toxicity study in rats treated with phthalimide. Adverse effects were not observed at 0.523 mg/l (~149 mg/kg/day), the highest dose tested. Due to the low vapor pressure (9.13×10^{-26} mmHg) and to the very low final use concentration (0.0138%), inhalation exposure and risk are believed to be negligible. In view of the proposed use pattern, dermal exposure is believed to be the significant route of exposure. No dermal toxicity study is available, therefore, an oral endpoint was used for risk assessment. A dermal absorption rate was assumed to be 100%. Exposure and risk assessments for commercial applicators (painters using airless sprayers) and for "homeowner"/residential applicators resulted in Margins of Exposure greater than 100 which do not exceed the Agency's level of concern.

Phthalimidomethyl copper phthalocyanine is not expected to be toxic to aquatic organisms. It is persistent in the environment. It is not expected to bioaccumulate.

After reviewing the available data, the Agency approves of the non-food use of phthalimidomethyl copper phthalocyanine as an inert ingredient as a copper pigment stabilizer in antimicrobial paint formulations at a final, end-use product concentration not to exceed 138 ppm (0.0138%).

References

MRID 49388001 Velea, L. and Patton, L. (2014) Submission Submission of a New Nonfood Use Inert Ingredient: copper, [29H,31Hphthalocyaninato(2-)-N29,N30,N31 ,N32]-, (1,3-dihydro-1,3-dioxo-2Hisoindol-2-yl)methyl derivatives (CAS# 68411-06-3).

MRID 49388002 Organization for Economic Cooperation and Development (OECD)(2005) Phthalimide. Screening Initial Assessment Report for SIAM 2.

MRID 49388003 Organization for Economic Cooperation and Development (OECD)(1993) Screening Information Data Set for copper phthalocyanine CAS 147-14-8.